Matthew B. Van Hook
DEPUTY GENERAL COUNSEL

PhRMA

September 15, 2000

BY MAIL AND E-MAIL

Mr. Tokuo Yoshida
Chief, Regulatory Control Unit
Programme on Substance Abuse
World Health Organization
20, Avenue Appia
CH-1211 Geneva 27
Switzerland

Dear Mr. Yoshida:

Re: International Drug Scheduling; Convention on Psychotropic Substances (U.S. FDA, Docket No. 00N-1257, Notice of April 28, 2000)

This acknowledges receipt of your communication dated July 18, 2000, responding to the Pharmaceutical Research and Manufacturers of America ("PhRMA") submission in response to the Federal Register notice, 65 Fed. Reg. 24, 969 (Apr. 28, 2000), concerning the September meeting of the World Health Organization ("WHO") Expert Committee on Drug Dependence ("ECDD"). We are very pleased that you have reached out to us in this manner, because we recognize the value of the work of WHO and the ECDD, and believe that dialogue will enhance the ability of these organizations to accomplish their missions.

Medical Availability

You ask whether PhRMA has a view concerning the effect on the medical availability of diazepam if it were transferred from Schedule IV to Schedule III under the Convention on Psychotropic Substances of 1971. First, it should be understood that PhRMA's interest in the scheduling process is not focused on any particular product. The industry's commitment to the Convention system is long-standing, and our foremost concern is that the system be open, fair, and technically sound. Respect for the system must rest on a bedrock of unassailable scientific and medical methodologies.

00N-1257 *Pharmaceutical Research and Manufacturers of America* C6

1100 Fifteenth Street, NW, Washington, DC 20005 • Tel: 202-835-3513 • FAX: 202-835-3592 • E-MAIL: mvanhook@phrma.org

The U.S. Drug Enforcement Agency ("DEA") gave no reason for its view that there would be no impact on medical availability of diazepam, if the considered schedule change were made. We assume therefore that this is because such a change in the international scheduling would not require the U.S. to reschedule diazepam from Schedule IV under our national law. Note, however, that expert opinion holds that rescheduling does affect physician prescribing practices and may cause unwarranted concern among the patient population. See, e.g., Transcript of Food and Drug Administration ("FDA") Public Hearing on Appropriate Scheduling of Benzodiazepines at 323-24 (Sept. 11, 1997) (Testimony of Dr. James Ballinger, American Psychiatric Association) (stating that the public is prepared to believe the worst about drugs and rescheduling even one benzodiazepine would cause the public to conclude that they were "dangerous drugs.") Therefore, because international rescheduling into the more restrictive Schedule III would send a signal of increased concern among the international community about diazepam, however inappropriate that signal might be, physicians and patients throughout the world, including the U.S., would be affected.

The WHO Questionnaire

PhRMA commented that the questionnaire, used by WHO to develop the information concerning the subject drugs from the member states and others, was not adequate for its purpose. Your response states that the questionnaire is kept as "simple as possible" in order not to burden the governments that are asked to respond.

We appreciate the need to avoid placing unnecessary requirements upon governments. On the other hand, we are mindful that the scheduling process is important to some degree for nearly everyone on the earth, touching as it does the ability of medical practitioners to do their work. WHO's medical and scientific judgments are an essential element to the process, and there is no doubt that the reports of member states and others, made in response to the questionnaires, are an indispensable factor in the making of those judgments. For the ECDD to be able to provide the proper technical advice, it must be given good data, including the information from the member states. The questionnaire used by WHO will not elicit the information needed for an informed, evidence-based judgment. We cannot accept that the convenience of member states is a good reason to abandon the scientific process.

Frank L. Hurley, Ph.D., a noted biostatistician, has examined the WHO questionnaires and concludes that the questionnaire is inadequate for the objective of obtaining data about the nature and extent of substance abuse. (See attached Declaration).

The questionnaires encourage the submission of anecdotal information, where accuracy dictates that data be obtained from structured studies or surveys. The information that will be obtained through the questionnaires is not amenable to the type of serious scientific analysis necessary for the WHO to make well-reasoned and informed medical/scientific judgments.

We believe that the member states, if educated as to the need for useful responses, would accept and respond to questionnaires that are designed to gather data that might be used for evidence-based decisionmaking. Perhaps the experience gained by the International Narcotics Control Board, which uses questionnaires in its work, could be helpful to WHO.

Therapeutic Usefulness

Your letter addresses the PhRMA comment that noted the absence of questions, in the questionnaires sent to the member states, about the therapeutic usefulness of diazepam and zolpidem.

i) Diazepam

You refer to the fact that the International Federation of Pharmaceutical Manufacturers Associations ("IFPMA") sent observers to the September, 1999 meeting where the WHO review guidelines for the ECDD were discussed and state that information from that meeting shows that the therapeutic usefulness of diazepam "does not need to be questioned or re-evaluated." We have seen the text of the ECDD guidelines that WHO is using. This text does not state that essential drugs are to be considered of "moderate to great" therapeutic usefulness, nor does it provide the criteria to establish therapeutic usefulness for a drug to be considered "essential."

The ECDD describes "essential drugs" as those that have been identified as providing safe and effective treatment for the infectious and chronic diseases affecting the world. Notwithstanding that the ECDD guidelines are silent about the criteria used to determine whether a drug is "essential," we agree that it is appropriate to consider diazepam, as an essential drug, as a drug for which there is "moderate to great" therapeutic usefulness.

Even though WHO recognizes the "moderate to great" usefulness of diazepam, it should be of considerable interest to the ECDD to know the conditions for which the drug is

currently being used in the member states. The purpose of the questionnaire is to give a current perspective of the use and abuse of the drug.

ii) Zolpidem

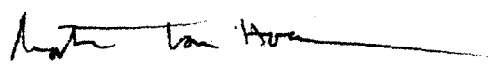
Zolpidem is not designated as an essential drug and the questionnaire does not ask about its therapeutic usefulness. Presumably WHO expects the ECDD to evaluate the therapeutic usefulness of this drug without hearing from the member states. We do not believe that the ECDD can conduct an adequate evaluation without the benefit of the data from the member states.

PhRMA's initial comments, and these, are offered in the belief that the work of WHO will be improved by opening up its processes to all participants, and the public. This dialogue concerning the questionnaires used by WHO has certainly been informative.

In order to make the record of this useful exchange as complete as possible, we are submitting your letter and this document to the public record, FDA Docket No. 00N-1257, opened by the U.S. government in the Federal Register announcement concerning the ECDD meeting.

Thank you for your attention to this matter.

Sincerely,



Matthew B. Van Hook
Deputy General Counsel

Enclosure
- Declaration of Frank L. Hurley, Ph.D.

cc (with T. Yoshida e-mail to M. Van Hook/PhRMA of July 18, 2000):
U.S. FDA Dockets Management Branch (HFA-305),
Docket No. 00N-1257
Corrine P. Moody, CDER (HFD-009)

NOTE

From: <yoshidat@who.ch>
To: <mvanhook@phrma.org>
Date: 7/18/00 12:15PM
Subject: Your letter to FDA dated May 15

Dear Dr Van Hook,

I have received from the US government PHRMA's comments on international drug scheduling. I have one question concerning the potential impact of transferring diazepam from Schedule IV to Schedule III. DEA's view was that there would be no impact on its medical availability. Does the Phrma have any view on this?

Let me take this opportunity to respond to some of the questions you raised. Re the WHO questionnaire, the more detailed the questions are the greater the burden on the governments to respond. For this reason, we are always requested to make our questionnaire as simple as possible.

Concerning the absence of questions about the therapeutic usefulness of diazepam or zolpidem, please refer to page 15 of the comments of Hoffmann-La-Roche. According to the scheduling criteria, Schedule III should include psychotropic substances with "moderate to great" therapeutic usefulness. Diazepam being an "essential drug", there will be no question about its therapeutic usefulness being higher than the average (from moderate to great). The only discussion point would therefore be whether the degree of seriousness of the public health or social problem is "significant" or "substantial". If it is "substantial", the drug would go to Schedule III. If it remains to be "significant", it should stay in Schedule IV.

IFPMA was fully involved in the discussion of the WHO review guidelines, including the scheduling criteria mentioned above, in September last year. If IFPMA had communicated the information it had on the scheduling criteria to Phrma, it would have been obvious to you that therapeutic usefulness of diazepam does not need to be questioned or re-evaluated this time.

Best regards,

Tokuo YOSHIDA
Secretary
32nd Expert Committee on Drug Dependence
EDM/QSM
WHO

DECLARATION OF FRANK L. HURLEY, PH.D.

I, Frank L. Hurley, Ph.D., declare and state as follows:

1. I make this declaration to provide my expert opinion in clinical epidemiology regarding the World Health Organization's ("WHO's") Questionnaires used for the collection of information and data for the WHO's review and ultimate scheduling recommendation for diazepam, zolpidem and ephedrine. The facts contained herein are true to the best of my knowledge, information and belief.

CREDENTIALS

2. I have worked in the field of clinical epidemiology for approximately 30 years. I received a Bachelor of Science degree in Mathematics and Pre-Medical Sciences from Georgetown University in 1966 and a Ph.D. in Biostatistics from Johns Hopkins University in 1970. I currently serve as an Adjunct Associate Professor for the Georgetown University School of Medicine. I am affiliated with a number of professional organizations, including, but not limited to, The Johns Hopkins University Health Advisory Board of the School of Hygiene and Public Health, the Commonwealth of Virginia Biotechnology Research Park Authority Board of Directors (appointed by Governor George Allen); the Food and Drug Law Institute, the Society for Clinical Trials and the Society for Epidemiologic Research. A true and accurate copy of my *curriculum vitae* is attached hereto as Tab A.

3. As an employee of a major contract research company and independent consultant I have been responsible for Food and Drug Administration ("FDA") regulatory and clinical research policy, identification of areas of importance for scientific development and senior scientific staff requirements. I work with clients to develop regulatory research strategies designed to minimize the time for FDA approval, review protocols, analyze and interpret results for clinical studies, and develop presentation of results for FDA. I routinely interact with investigators and medical consultants on issues of research design and interpretation of results; and review quality control procedures and client clinical data processing systems. I present seminars for Research and Development staff on designing and conducting clinical research for regulated products.

4. I have been involved in over 300 clinical studies of pharmaceuticals, medical devices, and diagnostic products; occupational health studies; as well as a number of epidemiological studies on the long-term effects of drugs and medical devices. I have assisted in the design and implementation of computerized occupational health information systems.

5. I have authored or co-authored over 100 technical reports on epidemiologic and clinical research. These reports have included the health effects of various occupational exposures, as well as reports on clinical studies of drugs and devices. I also have presented these reports to a variety of FDA advisory panels.

WHO Questionnaires

6. On March 18, 1998, the FDA published a notice in the Federal Register requesting the submission of data or comments concerning the abuse potential, actual abuse, medical usefulness, and trafficking of three drug substances, one of which is ephedrine. International Drug Scheduling; Convention on Psychotropic Substances; Dihydroetorphine; Ephedrine; Remifentanil; Isomers of Psychotropic Substances, 63 Fed. Reg. 13,258 (Mar. 18, 1998) ("Ephedrine Notice") A true and accurate copy of the Ephedrine Notice is attached hereto as Tab B. The notice stated that information and comments collected would be used by WHO in determining whether to recommend that certain international restrictions be placed on these substances.

7. The Ephedrine Notice included a questionnaire asking for pertinent information for each substance for the following:

(1) Availability of the substance (registered, marketed, dispensed, etc.)

(2) Extent of abuse of the substance.

(3) Degree of seriousness of the public health and social problems associated with abuse of the substance.

(4) Number of seizures of the substance in the illicit traffic during the previous three years and the quantities involved.

(5) Identification of the seized substance as of local or foreign manufacture and indication of any commercial markings.

(6) Existence of clandestine laboratories manufacturing the substance.

Ephedrine Notice, 63 Fed. Reg. 13,258 (Mar. 18, 1998) (footnote omitted).

8. On April 28, 2000, the FDA published a notice in the Federal Register requesting the submission of data or comments concerning the abuse potential, actual abuse, medical usefulness, and trafficking of six drug substances, including diazepam and zolpidem. International Drug Scheduling; Convention on Psychotropic Substances; 4-Bromo-2, 5-dimethoxyphenethylamine (2C-B); Gamma-hydroxybutyric acid (GHB); 4-Methylthioamphetamine (4-MTA); N-Methyl-1-(3,4-methylenedioxyphenyl)-2-butanamine (MBDB); Diazepam (INN); Zolpidem (INN), 65 Fed. Reg. 24,969 (Apr. 28, 2000) ("Diazepam Notice"). A true and accurate copy of the Diazepam Notice is attached hereto as Tab C. The notice asked for information in response to a WHO Questionnaire containing the following items:

(1) Availability of the substance (registered, marketed, dispensed, etc.);

(2) Extent of the abuse or misuse of the substance;

(3) Degree of seriousness of the public health and social problems associated with the abuse of the substance (statistics on cases of overdose deaths, dependence, etc.); and

> (4) Any information on the nature and extent of illicit activities involving the substance (clandestine manufacture, smuggling, diversion, seizure, etc.).

In addition to the above, with regard to Diazepam (INN) report on:

> (5) The impact of transferring diazepam from Schedule IV to Schedule III of the Convention on Psychotropic Substances, 1971, and its effect on availability for medical use.

In addition to items 1 and 4 above, with regard to Zolpidem (INN) report on:

> (6) The impact of placing zolpidem in Schedule IV of the Convention on Psychotropic Substances, 1971, and its effect on availability for medical use.

Diazepam Notice, 65 Fed. Reg. 24,969, 24,970 (Apr. 28, 2000) (footnote omitted).

9. I have reviewed the WHO Questionnaires for ephedrine, diazepam and zolpidem. In my opinion, based on thirty years of experience in epidemiology, the questionnaires are entirely inadequate to capture valid data and information about the nature and extent of substance abuse. The structure of the current questionnaires precludes collection of quantifiable data amenable to analysis. The format of the questionnaires encourages anecdotal responses, which will not provide the type of data required to assess the potential problems associated with abuse, or the extent of the problems. The lack of specific definition of terms means that "substance abuse" will be subject to a wide variety of interpretations. This will render the collective responses meaningless without specification of what each individual respondent defines as substance abuse.

10. In order to be accurate, such information should come from structured studies or surveys. The studies should include specific definitions for categories of substance abuse, information on the sources of reports of abuse and protocols for primary data capture. The only useful information to be elicited by the questionnaire would come from protocol driven studies or reports from structured registries submitted as supplements to the questionnaire.

11. I have reviewed correspondence from Dr. Tokuo Yoshida, Chief, Regulatory Control Unit, Programme on Substance Abuse for the WHO. Mr. Yoshida explained that the questionnaire was oversimplified to minimize the burden on respondents. However, one of the fundamental principles of research is that if the burden of supplying reasonably accurate and appropriately detailed responses is too great, then the survey should not be conducted. It is entirely inappropriate to substitute convenience for scientific rigor as the basis for obtaining data to support critical decisions.

Signed this 7th day of August, 2000,